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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,741	11/14/2005	Hiroyuki Aburatani	392.1001	4248

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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/526,741	**Applicant(s)** ABURATANI ET AL.	
	Examiner Peter J. Reddig	**Art Unit** 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 09 January 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *09 January 2009*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *9 and 23-29*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Karen A Canella/
Primary Examiner, Art Unit 1643

Continuation of 11. does NOT place the application in condition for allowance because: Claims 9 and 23-29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lage et al. (Virchows Arch 2001 438:567-573, IDS), in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85: 4852-4856), further in view of Dillman et al.(Annals of Internal Medicine 1989, 111:592-603), further in view of Mast et al. (Biochem. J. 1997, 327: 577-583), and further in view of Midorikawa (Proc. Amer. Assoc. Can. Res. March 2002, 43:11 Abstract #53) for the reasons previously set forth in the Office Action of July 9, 20008, section 2-pages 3-5.

Applicants argue that Lage, at page 570, right-column, lines 9-15 and Fig. 1, discloses that Western-blot analysis of a stomach cancer cell line EPG85-257RNOV using the disclosed antibody Be-F4 revealed the analogous results as the Northern blot analysis of stomach cancer (See Lage, page 570, right-column, line 13-15). On the other hand, Lage discloses the Western-blot analysis and histological staining ofhepatocarcinoma (See Lage, page 571, left-column and right-column text and Figs. 2 and 4) and concludes that "HCC cells constantly showed a decreased staining intensity when compared with the staining signal obtained in noncancerous liver cells from the same section (See Lage, page 571, right column, line 1-4)" and "[i]n contrast to the non-neoplastic hepatocytes, the cellular p62 content was unambiguously reduced in all malignant cells." (See Lage, Abstract line 11-13).

Applicants argue that it is evident from the disclousre of Lage that GPC3 is not highly expressed in a protein level in hepatocarcinoma cells. Applicants argue that the disclosure of Lage is inconsistent with the disclosure of Midorikawa wherein GPC3 is highly expressed in HepG2 cells and hepatocarcinoma cells, and with the disclosure of Mast that GPC3 is expressed on the surface of HepG2 cells (Applicants note that Mast does not mention the level of expression). Therefore, Applicants respectfully submit that one of skill in the art would not look to combine the teachings of Lage, Midorikawa and Mast because they are inconsistent with each other.

Applicants argue that even if Lage discloses a GPC3 monoclonal antibody obtained using an oligopeptide of amino acids 537-556 of GPC3, one of skill in the art would not combine Lage with Midorikawa and Mast which provide opposite teachings from Lage. Thus, one of skill in the art would not look to combine these references, thus the present invention is not obvious from the inventions disclosed in these references.

Applicants' arguments have been carefully considerd, but have not been found persuasive. Although Lage et al. does not show that GPC3 is highly expressed, it does show that GPC3 is expressed in hepatocellular carcinomas. Thus given the combined teachings of Lage and Midorikawa which both teach that GPC3 is expressed in hepatocellular carcinoma and given that Mast et al. teach that GPC 3 is expressed on the cell surface of HepG2 cells, one of skill in the art would have been motivated with a reasonable expectatin of success of making recombinant humanized monoclonal antibodies that has a cytotoxic activity in vitro against the cell line HepG2 in the presence of complement or peripheral blood mononuclear cells in view of Steplewski and Dillman who teach how to make humanized monoclonal antibodies that have ADCC or CDC activity in the presence of complement or peripheral blood mononuclear cells.

Claims 9 and 23-29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Filmus et al. (US Pat App. Pub. 2005/0233392 A1 May 23, 2002), in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85: 4852-4856), further in view of Dillman et al. (Annals of Internal Medicine 1989, 111:592-603), further in view of Mast et al. (Biochem. J. 1997, 327: 577-583), and further in view of Midorikawa (Proc. Amer. Assoc. Can. Res. March 2002, 43:11 Abstract #53) for the reasons previously set forth in the Office Action of July 9, 20008, section 3-pages 5-7.

Applicants argue that t, the antibody 1G12, as disclosed in Filmus is also described in International Patent Publication W02007/137170, a copy of which is attached as Appendix A. International Patent Publication W02007/137170 discloses in paragraph [0202] that "The cytotoxic activities of the anti-GPC3 antibodies (1G12, 8H5) with a secondary antibody conjugate were evaluated on the Glypican-3 positive HepG2 and Hep3B cell lines." See International Patent Publication W02007/137170, paragraph [0202]. Applicants argue that the unconjugated antibodies (1 G12, 8H5) were not observed to have cytotoxic activity on these cell lines.

Applicants argue that in addition, Applicants submit herewith a Data Sheet, attached as Appendix B (also available from the website http://www.biomosaics.com/pdfs/B0134R%20%20data%20sheet%202007, pdf), the antibody 1 G12 is distributed in a commercially available manner, and a person skilled in the art can easily confirm that the antibody 1 G12 does not have cytotoxic activity against hepatocarcinoma cells such as HepG2 cell line.

Applicants argue that in the Office Action, the Examiner alleged inter alia that it was obvious for a person skilled in the art to humanize the monoclonal antibody 1 G12 which strongly bind to human hepatocarcinoma cells using the humanizing techniques disclosed in Steplewski to create a humanized antibody having cytotoxicity (see page 7, line 4-15 of the Office Action). However Applicants argue that although Steplewski teaches that the mouse monoclonal antibody CO 17-1A having cytotoxicity may be humanized to overcome the problem of short half-life and immunogenicity, Steplewski fails to disclose that a mouse monoclonal antibody having no cytotoxicity, e.g. 1G12 antibody, may be humanized to impart cytotoxicity.

Applicants argue that the Examiner also alleged that the antibody of Filmus which binds to the amino acids 375-580 of GPC3 was known, and humanized techniques of antibodies as well as humanized antibodies having cytotoxicity were well known in the art, and thus one would prepare a humanized monoclonal antibody against a peptide having the amino acids 375-580 of GPC3 with a reasonable expectation of success (see page 7, line 8-15 of the Office Action). Applicants argue that as discussed above, however, since it was well known in the art, or one could easily understand, that the antibody ofFilmus, 1G12 antibody, does not have cytotoxicity, a person skilled in the art could not have been motivated from Steplewski to prepare a humanized antibody having cytotoxicity by humanizing a mouse monoclonal

antibody having no cytotoxicity. More likely, a person skilled in the art would recognize it difficult to prepare a humanized anti-GPC3 antibody having cytotoxicity based on Filmus that teaches the monoclonal antibody 1 G12 having no cytotoxicity.

Applicants argue that in addition, Filmus discloses that the antibody 1 G12 can detect GPC3 in serum (Example 6). Filmus teaches that GPC3 is released from hepatocarcinoma cells. Mast teaches that GPC3 is expressed on the surface of HepG2 cells and Midorikawa teaches that GPC3 level is elevated in HepG2 cells and 22 out of 52 hepatocellular carcinomas, while Filmus teaches that GPC3 expressed in that way is detected in serum. Accordingly, a person skilled in the art seeking to obtain an antibody having cytotoxicity with the aim of achieving treatment of hepatocarcinoma by damaging hepatocarcinoma cells would not look to combine Filmus with Mast and Midorikawa with a reasonable expectation of success, because Filmus discloses that GPC3 is detected in serum and, as discussed, the antibody 1 G12 cannot exert cytotoxicity against HepG2 cells.

Applicants argue that in conclusion, a person skilled in the art could not have conceived of the present invention based on the combination of the cited references.

Applicants arguments have been considered, but have not been found persuasive. Althougt the monoclonal antibodies of Filmus et al. do not have cytoxic activity by themselves, the claims are not drawn to monoclonal antibodies with inherent cytotoxic activity. W02007/137170 shows that the 1G12 and 8H5 antibodies can be used to induce cyotoxicity in HepG2 cells in the presence of the appropriate cytoxic stimuli, ie a drug conjugated secondary antibody, see Table 3 of W02007/137170. Thus humanized versions of the Filmus et al. monoclonal antibodies with complement or mononuclear cell reactive Fc domains would be expected to have cytotoxic activity towards HepG2 cells in the presence of complement or peripheral blood mononuclear cells. Although the monoclonal antibody of Steplewski had cytotoxic activity before humanization, given that it was well known in the art that the Fc portion of antibodies impart ADCC and CDC activity to an antibody, see Dilman p. 593, one of skill in the art would have a reasonable expectation of success of making the claimed monoclonal antibodies that have a cytotoxic activity in vitro against the cell line HepG2 in the presence of complement or peripheral blood mononuclear cells. Althought Filmus et al. teach that detection of GPC3 released in the serum, Filmus et al. also teach detection of GPC3 in the liver carcinoma tissue, see Tables 1 and 2 and Examples 4 and 5. Thus, given that both Filmus et al . and Midorikawa teach that GPC3 is expressed in hepatocellular carcinoma and given that Mast et al. teach that GPC 3 is expressed on the cell surface of HepG2 cells, one of skill in the art would have been motivated with a reasonable expectatin of success of making recombinant humanized monoclonal antibodies that has a cytotoxic activity in vitro against the cell line HepG2 in the presence of complement or peripheral blood mononuclear cells in view of Steplewski and Dillman who teach how to make humanized monoclonal antibodies that have ADCC or CDC activity in the presence of complement or peripheral blood mononuclear cells.